Chapter 6

Predicting Relapse and Outcome in First Episode Psychosis: Impact of Negative Symptoms, and Personalized Low Dose versus Maintenance Antipsychotic Treatment

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"If you walk through hell, keep going."
(Winston Churchill)

Abstract

Relapse of psychosis indicates worse functional outcome. The aim of most current treatment strategies is relapse-prevention, though neither predictors of relapse nor causation of functional decline has been established. If relapse were a consequence of a decline-related confounder, preventing relapse might only partly impact upon decline. We hypothesized baseline negative symptoms to predict both functional deficits and relapse risk. We examined: 1) what predicted relapse, 2) what predicted functional outcome and 3) if baseline negative symptoms (BNS) predicted relapse, whether medication strategies would make a difference reducing relapse rates. Post-hoc analysis of 7-year follow-up data of a first episode psychosis (FEP) cohort involved in a dose-reduction/discontinuation (DR) vs maintenance treatment (MT) trial (ISRCTN16228411). Patients (n=128) participating in the original trial, recruited from 257 FEP patients referred from October 2001 to December 2002 to 7 mental health care services in a 3.2 million population catchment area. After 7 years, 103 patients consented to follow-up assessment. In the original trial, patients were randomly

assigned after 6 months of remission to DR strategy or MT for 18 months. Thereafter, treatment was uncontrolled. Main outcome (functional outcome by treatment strategy) has been reported before. The hypotheses tested here were formulated after data-collection. Relapse was predicted by BNS and duration of untreated psychosis (DUP), and functional outcome was predicted by BNS, number of relapses and treatment strategy. Although all predictors had their unique contributions, BNS had the largest pseudo-partial correlation (r_{pp}) with the dependent variable in both models (r_{pp} = .60 for relapse and r_{pp} = .90 for functional outcome). Within MT, high levels of BNS were related to higher relapse rates. Within high and low BNS groups, relapse rates were equal across treatment strategies. BNS not only predicted non-recovery, but also relapses during 7-year follow-up. Apparent consequences of relapse, mainly non-recovery, have to be partially attributed to BNS. Relapse prevention by (low-dose) maintenance treatment does not seem effective, since relapse rates were equal across arms and depended only on BNS and DUP.

6.1 Introduction

Relapse in patients with a first psychotic episode (FEP) has been shown to be related to worse outcomes in many domains, including functional outcome (e.g. daily functioning, acquiring and maintaining a job, achieving educational goals, having meaningful relationships; Austin et al., 2015) and neurobiological outcome (e.g. brain structural integrity, cortical thinning; Andreasen, Liu, Ziebell, Vora, & Ho, 2013). Since this relationship has generally been assumed to be a causal one, e.g. by the conceivable impact of active psychosis on brain integrity, one of the most important goals of intervention programs in psychosis in recent years has been prevention of relapse. Maintenance therapy with antipsychotics has been shown to be the most effective intervention to reduce the short term risk of relapse, though stringent evidence for a robust effect of antipsychotics on long-term relapse prevention is lacking (Leucht et al., 2012a, 2012b). In addition, antipsychotic maintenance treatment has substantial drawbacks, and apart from extrapyramidal and metabolic side effects (De Hert, Detraux, van Winkel, Yu, & Correll, 2011; Lieberman et al., 2005; McEvoy et al., 2005; Salimi, Jarskog, & Lieberman, 2009) , antipsychotics have a negative impact on drive, curiosity, and reward-related behavior through their D2 receptor blockade (Artaloytia et al., 2006). Another potential drawback is evidence of accelerated shrinking of cortical thickness by antipsychotic drug exposure (Fusar-Poli et al., 2013; Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011; Lesh et al., 2015).

In a randomized trial by our group selected FEP patients who had been initially treated successfully with antipsychotics and achieved remission during 6 months, were randomized to either a treatment strategy of dose-reduction/discontinuation or (also low dose) maintenance treatment for 18 months. After 18 months, twice as many patients had experienced a relapse in the dose reduction/discontinuation group, compared to the maintenance group, only counterbalanced by a trending improvement in vocational functioning in the dose-reduction group (Wunderink et al., 2007). However, the relapse rates came on par from 3 years follow-up on, and by 7 years the patients who had previously been in the dose-reduction strategy showed twice the recovery rate of the maintenance patients. Thus, the initially higher relapse rates in the dose-reduction strategy did not have a decisive impact on long-term outcome, and because of equal long-term relapse rates in both treatment arms no conclusions could be drawn on the independent impact of relapse rates on functional outcome.

A causal link between relapse and functional deterioration has not been established in a strict sense. It is conceivable that a common factor could be causally related to both relapse and functional outcome, more or less explaining the apparent relation of relapse and unfavorable outcome. A functional brain disturbance, e.g. an excitation-inhibition imbalance in cortical areas (that might be due to lack of GABA-ergic parvalbumin interneuron activity (Chung, Fish, & Lewis, 2016) or

lack of glutamatergic input into that system (Coyle, Basu, Benneyworth, Balu, & Konopaske, 2012; Gonzalez-Burgos & Lewis, 2012; Moghaddam & Krystal, 2012)) might be causally related to both negative symptoms and exaggerated (disinhibited) ventral tegmental dopamine response in case of stress by a still unknown mechanism (Howes, McCutcheon, & Stone, 2015). Thus, this functional brain disturbance may lead to episodes of positive symptom experiences. If there is some truth in this hypothesis, it should be possible to predict relapses (positive symptom-exacerbations) by negative symptom levels at baseline (BNS). It has already been shown by a number of studies that low levels of BNS are a strong predictor of functional recovery, particularly in the long-term (Austin et al., 2015; Díaz-Caneja et al., 2015; McGorry et al., 2014; Wunderink et al., 2013). If, in addition, relapse would be predicted by BNS, it would mean that relapses are - at least partially - not the independent cause of worse functional outcome, but - to a certain extent - an epiphenomenon. It would also imply that relapse prevention at all costs would not be the right way to go, since it would be targeting a consequence rather than a cause of the disease.

The aim of this post hoc analysis was to test the hypothesis that levels of BNS predict both functional outcome and relapse risk. More specifically, we wanted to disentangle the effects of BNS and relapses on functional outcome and to investigate whether the relationship between relapse and outcome could be (partially) explained by BNS.

Post-hoc, we examined: 1) which factors predicted relapse, 2) which factors predicted functional outcome, and 3) if BNS predicted relapse, whether medication strategies would make a difference reducing relapse rates.

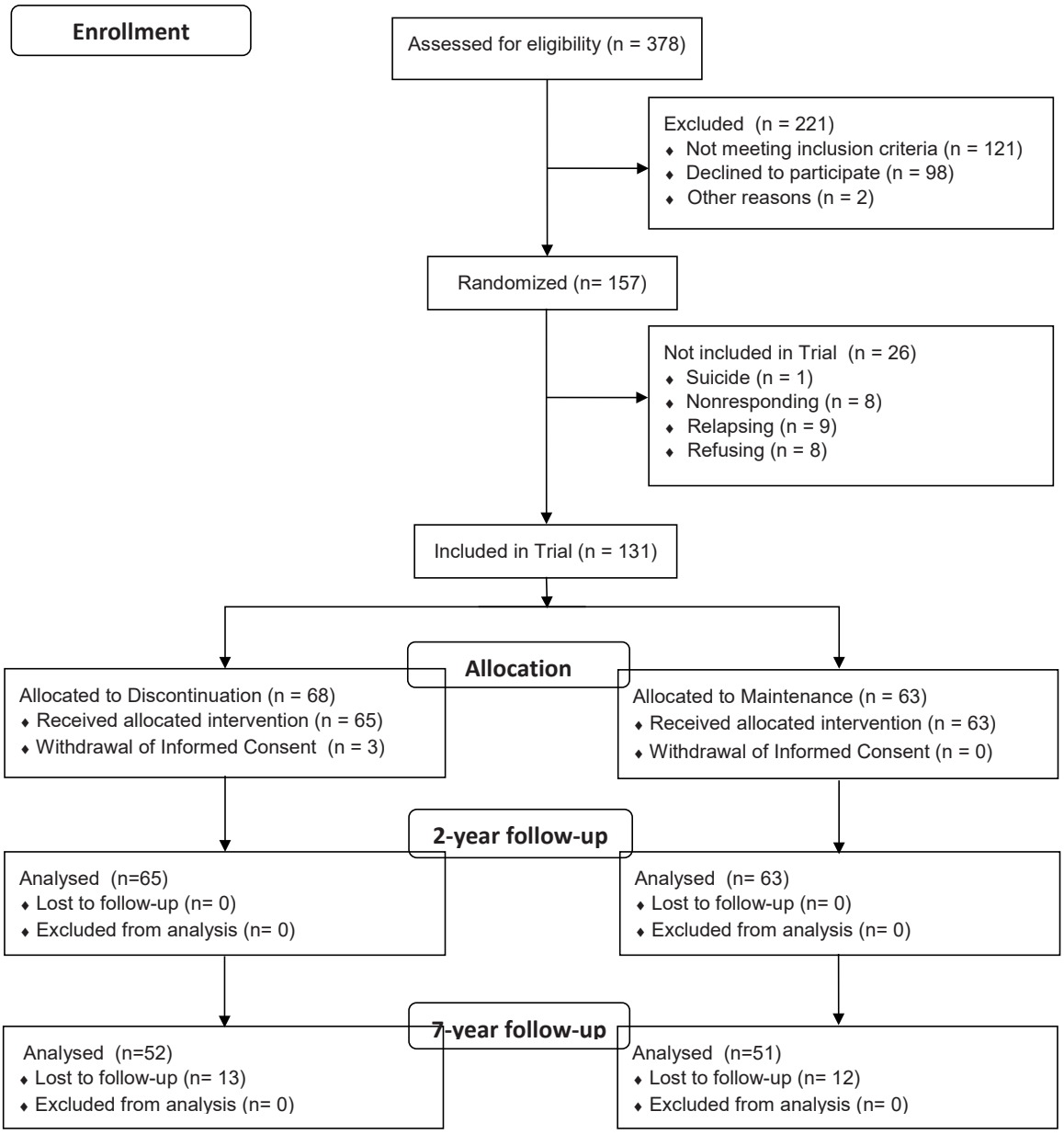
6.2 Methods

The details of the original and 7-year follow-up study have been described previously elsewhere (Wunderink et al., 2013; Wunderink et al., 2007). We used data collected at baseline and data collected during the follow-up to answer the new research questions formulated above.

6.2.1 Subjects

The patient flow-chart of the original 2-year trial and the 7-year follow-up study are depicted in Figure 6.1.

Figure 6.1 Flow Diagram of the original 2-year trial and the 7-year follow-up study.



Of the N = 378 patients that were initially screened, 257 met the eligibility criteria described more extensively by Wunderink et al. (2007). Patients seen for the first time in mental health care services because of a first episode of psychosis from October 1, 2001, until December 1, 2002 (N=257), in a 3.2 million-population catchment area were asked to participate in the original 2-year trial comparing DR with MT. It is important to note that all patients with a first episode psychosis who had a first contact with mental health care services were immediately anonymously registered by the research team to ensure no selection bias would occur because of selectively including patients. Only after the patients would have responded sufficiently to the prescribed antipsychotic medication they were asked for participation and consent. Of the 257 eligible FEP patients, 111 patients refused to participate or were lost to follow-up, and 18 patients did not show the required symptomatic response. A sustained positive symptom remission of a minimal duration of 6 months within 1 year after the start of antipsychotic treatment was required. This implied all relevant positive symptom scores on the Positive And Negative Syndrome Scale, (PANSS; Kay, Fishbein, & Opler, 1987) had to be continuously at or below the severity level of "mild" (score 3). One hundred twenty-eight patients were included in the original trial and completed it. Seven years after inclusion in the original trial, 103 patients were located and consented to a one-time follow-up assessment (Wunderink et al., 2013).

Of these 103 patients, 71 (68.9%) were male. The mean age at the end of the follow-up period was 26 years and 4 months (SD 6 years, 7 months). At baseline, 66 (64.1%) were living together with either a partner, parent or a relevant other, 45 (43.7 %) had a job for at least 16 hours a week, and 37 (35.9%) reported any drug or alcohol abuse or dependency.

6.2.2 Assessments and definitions

Baseline data were sampled as part of the original trial. For details see Wunderink et al. (2007). For the present post-hoc analysis, the following variables are relevant: sex, age, symptom severity (PANSS), social functioning, and duration of untreated psychosis (operationalized as the time interval between the first positive symptom experience and the start of antipsychotic treatment). Due to its skewed distribution, we used the log-transformed version of DUP (log-DUP) in the analyses.

Seven-year follow-up data included symptom severity using the PANSS, level of social functioning during the last six months of follow-up assessed by the Groningen Social Disability Schedule (GSDS; Wiersma, de Jong, Kraaijkamp, & Ormel, 1990), information regarding relapses (number of relapses, time to first relapse), and the type and dose of antipsychotics during the last two years of follow-up.

The definitions of the concepts used in the current study are the following:

Relapse: Operationalized by a two-step criterion: 1) clinician needs to adjust antipsychotics (increase dosage) or take any other measures (additional visits), and 2) any PANSS positive symptom item score was above 3 for at least one week.

Symptomatic remission: (a) Criterion to enter the trial (3 years before the Andreasen criteria were published): all PANSS positive symptom scores had to be continuously at or below the severity level of mild (score 3) during 6 consecutive months during the first year of treatment. (b) To evaluate the 7-year follow-up: the Andreasen criteria were used (selected PANSS item scores had to be at a level of mild (3) or less sustained for at least six consecutive months; Andreasen et al., 2005).

Functional recovery: Adequate functioning in the core domains of everyday life for at least six months. Adequate functioning was operationalized as only having ratings of either 'no' (0) or 'doubtful or some' (1) disability on six out of seven domains of the GSDS. For reasons of limited applicability, we decided to exclude the parenthood domain. The GSDS item scores range from 'no disability' (0) to 'severe disability' (3).

Recovery: Meeting the criteria of both symptomatic remission and functional recovery.

6.2.3 Statistical analyses

Descriptive information on sample characteristics have been reported elsewhere (Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013).

To determine which factors predicted relapse and which factors predicted functional outcome at the end of the follow-up period, we applied forward stepwise logistic regression analyses. Possible candidates as predictors were selected on the basis of findings reported in the literature and the hypotheses to be tested. In particular, for predicting relapse, treatment strategy, log-DUP, and BNS were the possible candidates, and for predicting functional outcome, treatment strategy, number of relapses, and BNS. For both logistic regressions, we computed pseudo-partial correlations in order to assess the unique contributions of the predictors in the final models.

In order to investigate whether BNS or medication strategies would be the key variable for predicting relapses, we divided the patients on the basis of their BNS severity into two categories (median-split): a low BNS group ($PANSS_{neg} < 13$, n = 54) and a high BNS group ($PANSS_{neg} > 12$, n = 49). Then we compared relapse survival rates within the treatment strategies (MT and DR) across low and high negative symptom levels, and relapse survival rates within BNS categories (low and high) across treatment strategies.

6.3 Results

6.3.1 Number of relapses and functional outcome

At the end of the follow-up period, the majority (68%) of the patients were symptomatically remitted, while only a minority (33%) were functionally recovered. Only 29% met both criteria and thus were considered fully recovered. In terms of odds ratios, we found a clear relationship between number of relapses and recovery: no relapse yielded an odds-ratio of one in two, one relapse an odds-ratio of 1 in 4, 2 relapses an odds-ratio of 1 in 5, and 3 or more relapses resulted in no recovery at all.

6.3.2 Predicting relapse

For relapse as the dependent variable (Table 6.1), the logistic regression model with log-DUP and BNS as independent variables was significant ($X^2(2) = 13.3$, $p < .001$, and Nagelkerke's pseudo $R^2 = .167$). The effect of treatment strategy ($X^2(1) = 0.1$, df=1, $p = .75$) on relapse was not significant when controlling for log-DUP and BNS. These two predictors had the strongest relationship with relapse and were therefore added to the model in the two previous steps. Longer DUP and more BNS increase the probability of a relapse to happen. In order to evaluate the unique contribution of each predictor, we computed pseudo-partial correlations between each predictor and the occurrence of relapse during follow-up (Hosmer, Lemeshow, & Sturdivant, 2013). The variance that is accounted for by (the) other predictor(s) is removed from both variables under investigation before computing the correlation. In addition, pseudo-partial correlations take the categorical nature of variables into account. The pseudo-partial correlations (r_{pp}) equaled $r_{pp} = .60$ for BNS and $r_{pp} = .31$ for log-DUP. Thus, the unique contribution of BNS when taking log-DUP into account was larger than vice versa.

Table 6.1 Logistic regression results for predicting relapse based on patients' characteristics.

Variables	***B***	***SE(B)***	***Wald* X^2**	***df***	***P***	e^B	***95% CI*** e^B
BNS	0.13	0.05	7.0	1	< .01	1.14	1.04, 1.26
Log-DUP	0.40	0.20	3.8	1	< .05	1.49	1.00, 2.22
Model X^2	13.3			2	< .01		
n	103						

BNS: Baseline Negative Symptoms; Log-DUP: log-transformed Duration of Untreated Psychosis.

6.3.3 Predicting functional outcome

In Table 6.2, the results of the logistic regression analysis for the dependent variable functional outcome are displayed. The model including treatment strategy, number of relapses and BNS as predictors was significant ($X^2(3) = 33.4$, $p < .01$, and Nagelkerke's pseudo $R^2 = .386$). MT, more relapses, and more BNS were predictive of worse functional outcome. The pseudo-partial correlations between each predictor and the criterion, controlling for the other two predictors in the model equaled $r_{pp} = .57$ for treatment strategy, $r_{pp} = .90$ for baseline negative symptoms and $r_{pp} = .64$ for total number of relapses. Thus, the unique contribution of BNS was greater than the contributions of either treatment strategy or number of relapses.

Table 6.2 Logistic regression results for predicting functional outcome based on patients' characteristics and treatment strategy.

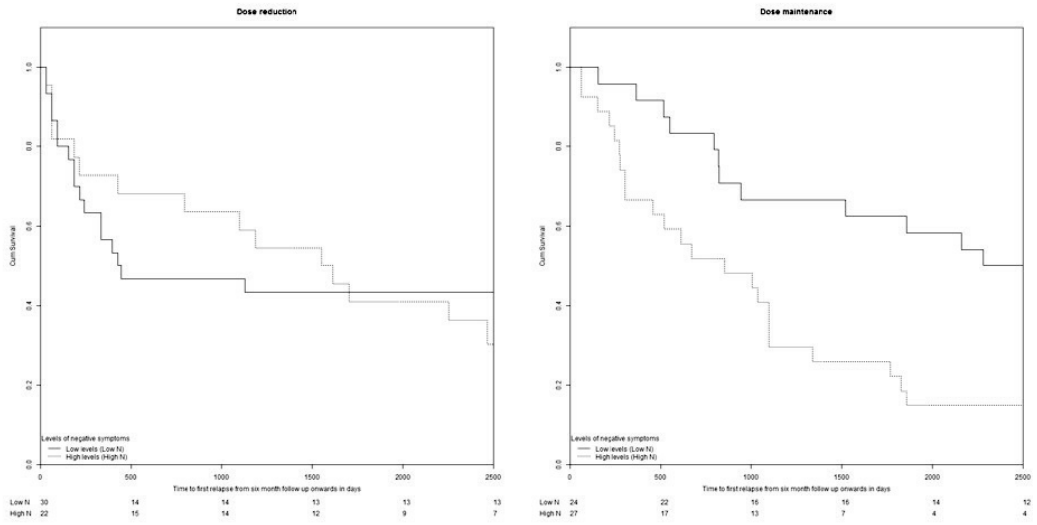
Variables	***B***	***SE(B)***	***Wald* X^2**	***df***	***P***	e^B	***95% CI*** e^B
Treatment strategy*	1.34	0.52	6.73	1	< .01	3.81	1.39, 10.47
BNS	-0.22	0.07	10.45	1	< .01	.81	0.71, 0.92
Number of relapses	-0.66	0.24	7.45	1	< .01	.52	0.32, 0.83
Model X^2	33.4			3	< .01		
N	103						

* Maintenance treatment (0) & Dose reduction (1); BNS: Baseline Negative Symptoms.

6.3.4 Disentangling the effects of baseline negative symptoms and treatment strategy on relapse risk

In Figure 6.2a-b, the survival functions representing relapse likelihood are displayed for the DR (left hand) and for the MT (right hand) strategy. The drawn lines represent the survival for low levels of BNS, and the dotted lines represent survival for high levels of BNS. Although the effect of BNS pooled over strata (treatment strategies) was significant (log rank $X^2 = 5.36$, df = 1, $p = .021$), indicating that more BNS are associated with higher relapse risk regardless of treatment strategy, the survival functions in 2a cross, so we present results for each stratum separately hereafter.

Figure 6.2a-b Survival functions for dose reduction/discontinuation (left-hand) and dose maintenance (right-hand).

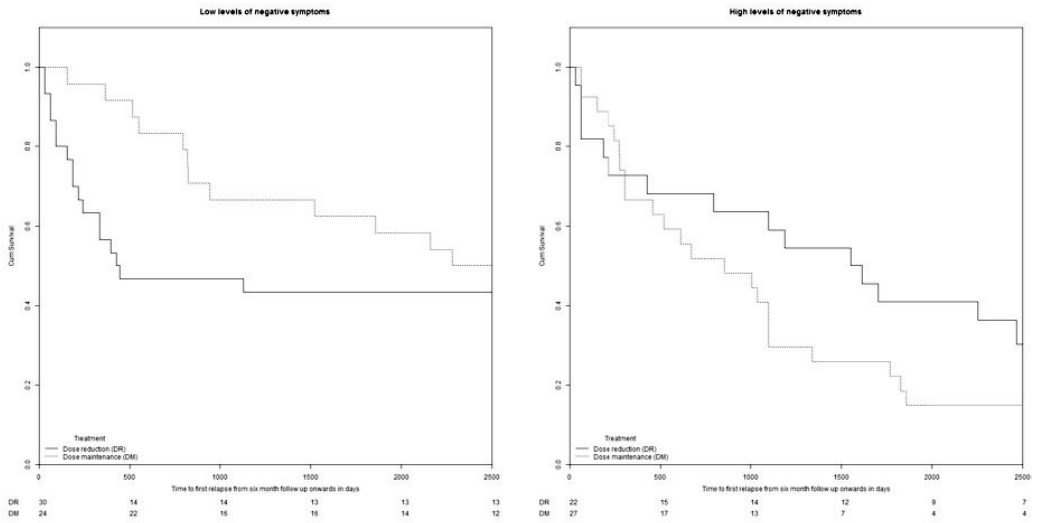


For the dose reduction/discontinuation treatment strategy, the differences in survival between low and high levels of BNS was not significant (log rank $X^2 = 0.1$, df = 1, p = .80). At the end of the follow-up period, the relapse rate for low BNS equaled 57% with a median of 427 days until relapse, and the relapse rate for high BNS equaled 68% with a median of 1553 days until relapse.

As can be seen from Figure 6.2b, for the maintenance treatment strategy, high levels of BNS are associated with a higher relapse risk during follow-up (log rank $X^2 = 9.0$, df = 1, $p < .01$). More specifically, at the end of the follow-up period, the relapse rate for low levels of BNS were 50% (median survival time 2282 days), while the relapse rate for high levels of BNS were 85% (median survival time 854 days).

In Figure 6.3a-b, the survival functions representing relapse likelihood are displayed for low (left hand) and high (right hand) levels of BNS. The drawn lines represent the dose reduction/discontinuation treatment strategy; the dotted lines represent the maintenance treatment strategy. Although difficult to infer from Figure 6.3a/b, the effect of treatment strategy pooled over strata (levels of BNS) was not significant (log rank $X^2 = 0.1$, df = 1, p = .79). Note that for low levels of BNS, MT seems more effective, while for high levels of BNS, DR seems advantageous.

Figure 6.3a-b Survival functions for low (left-hand) and high (right-hand) levels of baseline negative symptoms.



For low levels of BNS, the difference in survival between treatment strategies was not significant (log rank $X^2 = 1.6$, df = 1, p = .20). At the end of the follow-up period, the relapse rate for DR equaled 57% with a median of 427 days until relapse, and the relapse rate for MT equaled 50% with a median of 2282 days until relapse. The shorter median in DR reflects the earlier relapsing of subjects in this group compared to subjects in the MT group.

Also, for high levels of BNS, the difference in survival between treatment strategies was not significant (log rank $X^2 = 2.2$, df = 1, p = .14). Thus, although the differences in survival did not reach the level of statistical significance, differences between treatment strategies at end point were larger for high levels of BNS. More precisely, at the end of the follow-up period, the relapse rate for DR equaled 68% with a median of 1553 days until relapse, and the relapse rate for MT equaled 85% with a median of 854 days until relapse.

6.4 Discussion

6.4.1 Main findings

In the post hoc analyses described in this paper, we found that levels of baseline negative symptoms (BNS) are key (i) in predicting which individuals with a first episode of psychosis (FEP) will experience a relapse during a follow-up period of seven years, and (ii) in predicting these patients' levels of social and occupational functioning at the end of a long-term follow-up period. In addition to BNS, the log-

transformed DUP has been found to have incremental value for the prediction of relapse risk, longer DUP being associated with a higher risk of relapse. For predicting functional outcome, the number of relapses and treatment strategy have been found to have incremental value next to BNS, more relapses worsening functional outcome, and the dose reduction/discontinuation treatment strategy (DR) being positively related to better functional outcome compared to the maintenance treatment strategy (MT).

6.4.2 Our results in the light of existing literature and implications for treatment of FEP patients

The results of our study thus disagree with the notion that (number of) relapses would be most important for predicting functional outcome in patients with FEP (Emsley, Chiliza, & Asmal, 2013; Penn, Waldheter, Perkins, Mueser, & Lieberman, 2005; Sheitman & Lieberman, 1998; Wiersma, Nienhuis, Slooff, & Giel, 1998), and therefore more attention should be directed at prevention of these relapses (Haandel, Slooff, & van den Bosch, 2001). At first sight, the odds ratios for recovery conditional on number of relapses seemed to confirm the general assumption of relapse causing worse functional outcome. However, as previously stated, more detailed analysis showed the relationship of relapse and functional outcome to be more complicated, and to depend on levels of BNS, at least partially.

Furthermore, relapse rates were only higher in the DR strategy initially compared to MT. However, from 3-years follow-up on, the relapse rates came on par. In patients with low BNS, DR tended to effect higher relapse rates initially, but relapse rates equalized during the course of the full follow-up period. Regarding relapse rates, DR did not cause more relapses in the long term, though in patients with less severe negative symptoms relapse rates tended to be higher than in MT initially. This somewhat counterintuitive finding may also correspond to the finding by Gaebel et al., who found that patients who showed a most favorable first reaction to antipsychotic treatment appeared to respond worse to dose reduction than patients who did not show such a favorable reaction initially (Gaebel et al., 2015).

Though number of relapses has a unique negative impact on functional outcome, the association between BNS and functional outcome is much stronger. The importance of this finding might be that, though prevention of relapses is still of the utmost importance as one of few amenable factors in treating patients with schizophrenia-spectrum disorders, functional outcome will not only depend on the prevention of relapses but to a large extent on the preexisting negative symptoms. Thus, treatment aimed at improving functional outcome should address BNS next to relapse prevention. The fact that treatment strategy, particularly in patients with more severe negative symptoms, did not make a difference regarding relapse rates nor, in the long run, in the

subgroup of patients with low levels of BNS, might seem somewhat counterintuitive, since higher dosages of antipsychotics have a beneficial effect on relapse, as well as in preventing relapse in stabilized patients (Tiihonen et al., 2017). Though not significant, the survival curve of patients with high BNS in MT appears to show a less favorable downward course compared to DR strategy. A possible explanation might be that the MT strategy in our original trial was also a relatively low dose strategy, which may not be sufficient to prevent relapses in relapse-prone patients. The mean daily dose of haloperidol equivalents at 7 years of follow-up was 2.2 mg in the dose reduction strategy against 3.6 mg in the maintenance strategy. A question still unanswered is whether in patients with high levels of baseline negative symptoms, who are more relapse prone, higher dosages of antipsychotics than used in this trial might be beneficial to prevent relapses, and whether their levels of functioning would benefit or suffer from a higher dosage strategy than used in this trial. The same could be stated for the use of clozapine in this high BNS patient group. This would correspond to the guidelines that recommend clozapine in case of prominent negative symptoms, and to the results of the recent study by Tiihonen et al. (2017)

If negative symptoms would be a proxy for a biological basis of relapse-proneness (being suggestive of an ill-wired brain structure), it would be very important to adapt our staging approach in such a way as to incorporate negative symptoms in risk profiles (Wunderink, 2017). In addition, resources should be deployed to find optimal treatment strategies for patients with more severe negative symptoms in line with the aforementioned dilemma: to prevent relapses and thereby running a risk to limit initiative and drive, or to accept a certain relapse risk possibly in favor of not further jeopardizing already impaired functioning.

A limitation of our post-hoc analysis is that the original study has not been powered to detect significant differences in relapse rates between the DR and MT strategies within the high and low BNS groups. A lack of power may be one of the reasons why we did not find significant differences between the treatment strategies regarding relapse rates in the high and low BNS groups. Our results should be tested in larger, adequately powered trials.

6.5 References

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